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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,462	04/25/2001	Barbara A. Foster	PC10583ADAM	8327

7590

12/15/2004

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EXAMINER

COOK, LISA V

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/843,462

Applicant(s)

FOSTER ET AL.

Examiner

Lisa V. Cook

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4-8 and 20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4-8 and 20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/19/04 has been entered.

Amendment Entry

2. Applicants' response to the Final Office action mailed 5/17/004 is acknowledged. (Filed 17 September 2004). In the amendment filed 9/17/04, claim 1 was modified while claims 2-3, 9-19, and 21-23 were canceled. Currently claims 1, 4-8 and 20 are pending and under consideration.

3. Rejections and/or Objections not reiterated below have been withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 4-7 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350).

Wen et al. teach an ELISA (enzyme linked immuosorbent assay) to detect p110^{RB} (retinoblastoma protein). ELISA methods are taught in the instant specification (see page 6, figure 1) A coating antibody (anti-retinoblastoma protein (Rb) capture antibody) in combination with a 3C8 monoclonal antibody (anti-Rb primary antibody) is used to measure the retinoblastoma protein. See page 235, Section 3.3

Wen et al. differ from the instant invention in not specifically teaching the correlation of retinoblastoma protein to cyclin-dependent CDK activity.

However, Juan et al. disclose a method to measure the in situ phosphorylation state of retinoblastoma protein (pRb). This is accomplished by employing dual antibodies simultaneously to detect pRb. One antibody specifically detects underphosphorylated forms of the protein (pRb^P) and the other reacts with total (pRb^T).

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The conjugation of these anti-pRb mAbs with fluorochromes of different color, allows for multiparametered flow cytometry analysis. See page 105, 1st paragraph, 1st column. In the method human peripheral blood lymphocytes in culture are contacted with anti-pRb^T conjugated to CY-Chrome and anti-pRb^{P-} conjugated with FITC. (Please see page 105, 1st column, 2nd paragraph). The fluorescence measurement can be utilized to detect agents that target CDK4 activity or other CKDs activity in pRb phosphorylation activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure CDK activity as taught by Juan et al. with the retinoblastoma protein detection method of Wen et al., because Juan et al. taught that assays to detect retinoblastoma proteins "could be applied for screening ...CDKs and monitoring retinoblastoma phosphorylation". See abstract.

Juan et al. also taught that the function of pRb is affected by its phosphorylation at serine and threonine residues by the cyclin-dependent kinases. Page 104, 2nd column 1st paragraph.

One having ordinary skill in the art would have been motivated to correlate CDK activity in retinoblastoma protein detection in order to more obtain information with respect to the function of the protein.

Wen et al. in view of Juan et al. differ from the instant invention in not specifically teaching the measurement of CDK2 and CDK4 activity with a capture antibody recognizing site-specific phosphorylation sited like Ser612 or Ser780.

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However, Watanabe et al. disclose antibodies to detect the phosphorylation of retinoblastoma protein (pRb). Applicant's Rb protein. The formed complex was further employed to measure Cdk2 and Cdk4 kinase activities. See abstract. The reference teaches that pRb contains more than 12 phosphorylation sites at serine or threonine, and is phosphorylated by cyclin-dependent kinases (Cdks) in a cell cyclin-dependent manner. Page 342, 2nd column. Antibodies directed to Ser780 and Ser612 are taught on page 343 –2.3 Antibodies.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure Cyclin E/Cdk2 and Cyclin D/Cdk4 activity with known phosphorylation site-specific antibodies as taught by Watanabe et al. in the retinoblastoma protein detection method of Wen et al. in view of Juan et al., because Watanabe et al. taught that “recently, consensus motifs for phosphorylation by cyclin D/Cdk4 and cyclin E/Cdk2 were determined and antibodies against pRb phosphorylated sites were prepared”.... by Kitagawa et al. (page 343, 1st column, 2nd paragraph). Juan et al. further taught “little is known about the site specific phosphorylation of pRb in vivo during the differentiation process”. (page 343, 1st column, 2nd paragraph).

Therein one having ordinary skill in the art would have been motivated to employ the known Cyclin E/Cdk2 and Cyclin D/Cdk4 antibodies directed to known sites of the retinoblastoma protein (pRb) in order to understand cyclin dependent kinase activity (cdks) in a sample. The knowledge of site specific-antibodies enhanced sensitivity with respect to where the pRb protein is being phosphorylated, therefore none relevant sites are not evaluated giving more accurate and precise detection.

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II. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wen et al. (Journal of Immunological Methods, 169, 1994, 231-240) in view of Juan et al. (Experimental Cell Research, 239, 104-110, 1998) and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350) as applied to claims 1-7 and 20 above, and further in view of Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187).

Please see Wen et al. in view of Juan et al. and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350) as set forth above.

Wen et al. in view of Juan et al. and further in view of Watanabe et al. (Brian Research, 842, 1999, pages 342-350) differ from the instant invention in not specifically teaching the detection assay in test plates/micro titer plates.

However, Maggio disclose enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase/test plate. The solid phase can be particles, cellulose, polyacrylamide, agarose, discs, tubes, beads, or micro plates (micro titer plates). See page 186.

Wen et al., Juan et al., Watanabe et al., and Maggio are analogous art because they are from the same field of endeavor, all four inventions teach methods immunoassay methods.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use micro titer plates as taught by Maggio in the assay method to detection retinoblastoma protein of Wen et al. in view of Juan et al. and further in view of Watanabe et al. because Maggio taught that micro plates or micro titer plates "are very convenient to wash thereby reducing labor in assay procedures". Page 186, last line.

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Response to Argument

5. The Declaration of Barbara A. Foster and Farzan Rastinejad filed on 09 May 2003 under 37 CFR 1.131 has been considered but is ineffective to overcome the Watanabe et al., Brain Research 842:342-50, 1999 reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another. Conception is more than a vague idea of how to solve a problem.

The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The Declaration is not accompanied with exhibits of drawings or records, or photocopies thereof. Please see 37 CFR 1.131 Affidavit or declaration of prior invention.

b) The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. Original exhibits of drawings or records, or photocopies thereof, must accompany and form part of the affidavit or declaration or their absence satisfactorily explained.

In support of the Declaration, Applicant has provided a fax copy of a Patent Application submitted on June 10, 1999 to the Pfizer's New York Patent Department. Therein proving a conception and reduction to practice date of June 10, 1999. This was considered but not found persuasive because Watanabe et al. were cited to teach Cdk2 and Cdk4 site-specific antibodies. Watanabe et al. teach this concept as disclosed by M.Kitagawa and Y.Taya in 1996. See page 343 – 1st column 2nd paragraph and reference #15 on page 349. The concept taught by Watanabe et al. as disclosed by Kitagawa and Taya was reduced to practice as early as 1996 before Applicants June 10, 1999 date. Accordingly, the rejection is maintained.

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6. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant contends that the method do not teach phosphorylated Rb and CDK activity via Rb phosphorylation at specific residues by CDK (capture antibody). This argument was carefully considered but not found persuasive because Watanabe et al. teach Cdk2 and Cdk4 activity via phosphoylated Rb sites including Ser780 and Ser612 as recited in the instant claims. See page 343 2nd column - Antibodies.

The rejections above teach methods employing dual antibodies to Rb in various states (phosphorylated, underphosphorylated, and irrespective of phosphorylation) as a means for measuring CDK activity (Wen et al. in view of Juan et al.). Although the methods do not reciting the capture antibodies used by Applicant the commercially available antibody reagents are taught by Watanabe et al. The rejections including Maggio (Immunoenzyme technique I, CRC press © 1980, pages 186-187) are maintained in view of the response above. Accordingly the rejections are maintained.

7. For reasons aforementioned, no claims are allowed.

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8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.



Lisa V. Cook

Patent Examiner

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Remsen 3C-59

571-272-0816



**LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600**

12/11/04